IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of:		Docket No.:	06510003PB
Marshall Z. SCHWARTZ			
Serial No.:	09/931,112	Group Art Unit:	1631
Confirmation No.:	3767		
Filed:	August 17, 2001	Examiner:	Michael Borin

For: **TREATMENT OF INTESTINAL EPITHELIAL CELL MALFUNCTION, INFLAMMATION OR DAMAGE WITH HEPATOCYTE GROWTH FACTOR**

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF UNDER 37 C.F.R. § 41.37 (a)

Sir:

Pursuant to 37 C.F.R. § 41.31(a), Appellant filed a timely Notice of Appeal on January 25, 2005 from the Final Rejection in the Office Action, dated July 26, 2004, rejecting claims 7, 9-12 and 21-33 in this application. Pursuant to Rule 41.37(a), Appellant files one copy of this Appeal Brief.

The requisite appeal fee under 37 C.F.R. § 41.20(b)(2) in the amount of $250.00 for the filing of the Appeal Brief is being paid by check, submitted herewith, as well as a check and petition for a two-month extension of time, extending the time for filing the Appeal Brief through May 25, 2005. However, if for any reason the necessary fee is not associated with this file, the Commissioner is authorized to charge the fee for the Appeal Brief and any necessary extension of time fees to Deposit Account No. 23-1951.

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Additionally, Appellant believes that all disputed issues presented herein are appealable. However, if the Board of Patent Appeals and Interferences (BPAI) feels that the Examiner's refusal to consider the Rule 131 Declaration sufficient to antedate the references of record is petitionable instead of appealable, Appellant requests that this issue be considered as a petition under 37 C.F.R. § 1.181 requesting supervisory review of the Examiner's determination of the sufficiency of the Rule 131 Declaration. Please charge any Petition related fees to Deposit Account No. 23-1951.

In accordance with 37 C.F.R. § 41.37(c)(1), Appellant submits the following:

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is The Nemours Foundation, assignee of the entire interest in the above-identified application.

II. RELATED APPEALS AND INTERFERENCES

The Appellant, Appellant's legal representatives and the Assignee are not aware of any appeals, interferences or judicial proceedings that are related to, directly affect, or are directly affected by or have a bearing on the BPAI's decision in this Appeal.

III. STATUS OF THE CLAIMS

Claims 7, 9-12 and 21-33 are pending in the application and have been finally rejected in the Final Office Action of July 20, 2004 ("Final Office Action"). Claims 1-6, 8 and 13-20 have been cancelled. Claims 7, 9-12 and 21-33 are the subject of this Appeal. A copy of the appealed claims is provided in the Claims Appendix attached herewith.

IV. STATUS OF AMENDMENTS

No amendment has been filed subsequent to the final rejection. However, a Reply under 37 C.F.R. § 1.116 was filed on January 25, 2005, subsequent to the issuance of the Final Office Action, which requested reconsideration of the application in light of a Declaration under 37 C.F.R. § 1.131 of the inventor, Dr. Schwartz, and the accompanying remarks filed therewith. The Rule 131 Declaration antedated three of the four references relied upon in the Final Rejection. In a first Advisory Action issued on March 1, 2005, the Examiner indicated that the Rule 116 Reply was considered but did not place the application in condition for allowance; and additionally, the Examiner did not allow entry the Rule 131 Declaration based upon 37 C.F.R. § 116(e). The basis for refusal to enter the Rule 131 Declaration was the asserted failure by Applicant to make a proper showing as to why the Declaration was not presented earlier. (Advisory Action of March 1, 2005.) Subsequent to a telephone interview with the Examiner, at which time Applicant's representative made a persuasive argument as to the impropriety of the Examiner's refusal to enter the Rule 131 Declaration, i.e., that the need for the Declaration only became evident after the Examiner's position taken in the Final Office Action, the Examiner issued a Supplemental Advisory Action dated March 22, 2005, which entered the Rule 131 Declaration. However, the Examiner improperly deemed the Declaration insufficient to

overcome the Final Rejection for the reasons discussed below.[1] A copy of the Rule 131 Declaration appears in the Evidence Appendix attached hereto.

V. SUMMARY OF CLAIMED SUBJECT MATTER

There are three independent claims in this case: claims 7, 21 and 26. The following descriptions include references to particular parts of the specification, as required by the Rules. However, these descriptions and references to the specification are merely exemplary and there may be other portions of the disclosure that also support these claims. Accordingly, these descriptions should not be considered as a surrender of claim scope or any other aspect of the invention defined by these or other claims.

The invention relates generally to the treatment of inflammatory bowel diseases in a patient and, more particularly, to the therapeutic effects of treating a patient having an inflammatory bowel disease condition with Hepatocyte Growth Factor ("HGF"). (*See, e.g.*, Specification at p. 1, lines 6-8, p. 2, lines 9-11.)

Two prior parent patents relating to this subject matter already have issued to the inventor of this application. *See* U.S. Patent 5,972,887 to Marshall Z. Schwartz entitled "Treatment of Intestinal Epithelial Cell Malfunctions with Hepatocyte Growth Factor" and U.S. Patent 6,319,899 to Marshall Z. Schwartz entitled "Method of Composition for the Treatment of Inflammatory Bowel Disease." The claims at issue in the appeal are directed to other, related aspects of Dr. Schwartz's work in this field, as described below. The Examiner has already determined that the claims at issue in the application are patentably indistinct from the claims of its parent U.S. Patent No. 5, 972,887 and required Appellant to file a terminal disclaimer to

[1] This is another example of the improper piecemeal prosecution that has plagued this application and cost the Appellant and the assignee dearly in terms of unnecessary costs and undue delay. *See, e.g.*, the Preliminary Comments at pp. 4-6 of the Reply Under 37 C.F.R. § 116, filed January 25, 2005.

overcome the Examiner's double patenting rejection over the claims that issued in that parent U.S. patent. (*See* Office Action dated October 19, 2003; Final Office Action dated July 26, 2004 and Terminal Disclaimer filed on January 25, 2005.) Of course, the obviousness rejection at issue in this appeal, which is based upon the very same prior art distinguished in the parent patent, is flatly inconsistent with the Examiner' double patenting finding. If the claims of this application and the patent are patentably indistinct, as the Examiner already found, they must also be allowable as the same prior art is relied upon in both cases.

A. Independent Claim 7

Inflammatory Bowel Disease ("IBD"), including conditions known as Chronic Ulcerative Colitis ("CUC") and Crohn's Disease ("CD") are devastating disorders with unknown etiology. (*See, e.g.,* Specification at p.1, lines 9-11.) IBD conditions can cause intestinal mucosal damage. Independent claim 7 relates to a method for treating a patient having intestinal mucosal damage comprising decreasing the mucosal damage of the intestine by administering an effective dose of HGF to the patient where the patient has a condition including Chronic Ulcerative Colitis, Crohn's Disease, necrotizing enterocolitis, severe acute gastroenteritis, chronic gastroenteritis, cholera, and chronic infections of the bowel. (*See, e.g.,* Specification at page 2, lines 13-22; page 3, lines 13-17; and page 4, line 15 through page 6, line 16.) Specifically, for example, decreasing mucosal damage may include reducing and preventing gross histological lesions as well as reducing intestinal inflammation in a patient caused by IBD. (*See, e.g.,* Specification at page 3, lines 18-21.)

B. Independent Claim 21

Independent claim 21 relates to a method for treating a patient having intestinal mucosal damage comprising decreasing the mucosal damage of the intestine by administering an effective dose of HGF to the patient wherein the patient has a condition selected from the group consisting of immunologic disorders affecting the intestine, immunodeficiency syndromes affecting the intestine, and HIV. (*Id.* at page 2, lines 13-22; page 3, lines 13-19; and page 4, lines 1-3; and page 4, line 15 through page 6, line 16.)

C. Independent Claim 26

Independent claim 26 relates to a method for treating a patient having intestinal mucosal damage comprising decreasing the mucosal damage of the intestine by administering an effective dose of HGF to the patient wherein the effective dosage range of HGF is about 30 μg/kg body weight/day to about 300 μg/kg body weight/day. (*Id.* at page 2, lines 13-22; page 3, lines 4-7, 13-19; and page 4, line 4 through page 6, line 16.)

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL.

Claims 7, 9-12 and 21-33 stand rejected under 35 U.S.C. § 103(a) as being obvious over Zushi et al., 270(5 Pt 1) AM. J. PHYSIOL., G757-62 (1996) ("Zushi") and Japanese Patent Application Publication No. 8-231418, Published September 10, 1996 ("Ishii") and Fukamachi et al., 205(2) BIOCHEM. BIOPHYS. RES. COMMUN. 1445-51 (1994) ("Fukamachi") and Halttunen et al., 111(5) GASTROENTEROLOGY 1252-62 (1996) ("Halttunen"). The grounds of rejection have not changed from the first Office Action on the merits, dated October 21, 2003, which is itself a copy of the rejection made in parent application Serial No. 08/932,931, Paper No. 8, dated January 21, 1999, which application matured into the U.S. parent patent noted above. This rejection is discussed in the argument section below.

VII. ARGUMENT

A. Traversal of Rejection of Claims 7, 9-12 and 21-33 Under 35 U.S.C. 103(a) as Being Unpatentable Over Zushi and Ishii and Fukamachi and Halttunen

1. Rejection of Independent Claims 7 and 21

The rejection of claims 7 and 21 under 35 U.S.C. § 103(a) as being unpatentable over Zushi and Ishii and Fukamachi and Halttunen is in error and the decision of the Examiner to finally reject this claim should be reversed.

In the October 21, 2003 Office Action, incorporated by reference in the Final Rejection, the Examiner relies upon all four references and alleges that "[t]aken together, the prior art demonstrates that HGF, in several cell culture models, stimulate proliferation of intestinal cells and augmentation of their motility." (*Id.* at 4.) The Examiner admits that "the referenced prior art does not demonstrate, directly, the *in vivo* effects as claimed." (*Id.* at 5.) But he nonetheless concludes that it:

> would have been *prima facie* obvious, however, to one skilled in the pertinent art that such effect of HGF demonstrated on cellular level would *in vivo* translate into the increase in intestinal tissue mass and enhancement of intestinal functions, such as absorptive function. This, in turn would result in decrease in the extent of mucosal damage in the diseased intestine, i.e., in the effect instantly claimed. In view of the above, one of ordinary skill in the art would have been motivated to use HGF a therapeutic agent for increasing intestinal tissue mass and augmenting its functions.

The Examiner's conclusions are wrong. First, three of these four references are not valid prior art references because they were antedated by the Rule 131 Declaration entered by the Examiner. In finding the Declaration insufficient to overcome the rejection, the Examiner has engaged in completely circular reasoning and has failed to follow the explicit direction in the MPEP, as discussed below.

Secondly, none of these references, even if they all constituted prior art, whether taken singly or in combination, disclose or suggest each and every limitation of claims 7 and 21, including at least the limitation requiring decreasing mucosal damage in the intestine by administering an effective dose of HGF. Thus, even if the combination of Zushi and Ishii and Fukamachi and Halttunen were proper, it would still fail to disclose or suggest the claimed inventions.

a. The Rule 131 Declaration Moots the Rejection By Removing Three of Four References Relied Upon by the Examiner

The Rule 131 Declaration established that Appellant's claimed invention antedates the Zushi, Ishii and Halttunen references relied upon in the Final Rejection, and therefore moots the rejection. The Examiner's reasoning in the Advisory Action dated March 22, 2005 for deeming the Declaration insufficient is completely circular and contravenes MPEP § 715.02.

First, the Examiner presumably considers all three of these references to qualify as prior art under 35 U.S.C. § 102(a) because their publication dates are less than one year prior to the September 19, 1996 effective filing date of this application. Specifically, the Zushi reference has a publication date of May 1996, the Ishii reference has a publication date of September 10, 1996, and the Halttunen has a publication date of November 1996. The application at issue in this appeal is entitled to benefit of the September 19, 1996 priority date of U.S. Application Serial No. 08/932,391 because this application is a divisional application of U.S. Application Serial No. 09/395,129, filed on September 14, 1999, now U.S. Patent No. 6,319,899, which in turn is a continuation-in-part application of U.S. Application Serial No. 08/932,391, now U.S. Patent No. 5,972,887, which claims priority to provisional application Serial No. 60/026,352, filed on September 19, 1996 (the '252 provisional application).

The Examiner has cited these references of record for the teaching that HGF stimulates the proliferation, motility and growth of intestinal cells *in vitro*. For example, on page 4 of the Final Office Action, the Examiner states "[t]he references used in the rejection demonstrate that HGF causes proliferation of intestinal cells," and on page 3 of the Final Office Action, the Examiner states "[t]he rejection combined several references to demonstrate that HGF has similar proliferative effect on different cell systems." (emphasis added.) The Examiner has not cited any of the references for the teaching of decreasing mucosal damage in a patient by administering an effective dose of HGF as required by claims 7 and 21.

The '252 provisional application discloses the administration of an effective dose of HGF as a treatment for patients afflicted with inflammatory bowel disease, such as Crohn's disease and ulcerative colitis. (*See e.g.*, '252 provisional application at page 5, lines 1-28.) Furthermore, the '252 provisional application discloses that administration of an effective dose of HGF stimulates growth and proliferation of intestinal cells *in vivo*. (*See id.* at 8, lines 19-22.) Thus, the '252 provisional application supports the pending claims and establishes that the Zushi, Ishii and Halttunen references are not available as prior art under 35 U.S.C. § 102(b). Therefore, these references may be removed as prior art by filing of a Rule 131 Declaration.

In the Rule 131 Declaration entered by the Examiner, Dr. Schwartz has provided as Exhibit E a copy of an abstract (date redacted) he authored with the assistance of his research assistants. The abstract was submitted to the American Academy of Pediatrics Section on Surgery, but does not constitute a bar against this application. (¶6.) The abstract describes research work done in Dr. Schwartz's laboratory, and evidences that Dr. Schwartz reduced to practice in the United States the inventions disclosed and claimed in this application before the publication dates of the three references at issue.

The experimental data and information summarized in the abstract is contemporaneous evidence of the reduction to practice of the claimed invention in the United States. (¶7.) In particular, the abstract summarizes a study designed to examine the effect of systemically administered HGF on intestinal mass and function in adult male rats. (¶8.) Specifically, following a 14 day infusion period where the rats were administered either saline, 75 μg/kg/d of HGF, 150 μg/kg/d of HGF, or 300 μg/kg/d of HGF, mucosal DNA content and protein content was analyzed in a segment of the mid small intestine for each group. (*Id.*) The results of the study demonstrated for the first time that HGF can stimulate cell proliferation of intestinal epithelial cells *in vivo*. (*Id.* and *see, e.g.*, Rule 131 Declaration, Exhibit E stating "Conclusion: These data demonstrate for the first time that HGF can increase intestinal epithelial cell function and stimulate cell proliferation *in vivo*. HGF may be clinically useful in patients with Short Bowel Syndrome.")

In the second Supplemental Advisory Action dated March 22, 2005, the Examiner improperly deemed the Rule 131 Declaration insufficient by requiring Appellant to show reduction to practice of more than what the cited references teach.[2] Specifically, the Examiner stated that the "claims are directed to method of treating a patient having mucosal damage," and the abstract discussed in the Rule 131 Declaration "does not demonstrate reduction to practice of the claimed invention as it describes effect of HGF on normal healthy rats as compared to patients having mucosal damage addressed in the instant claims." (Advisory Action dated March 22, 2005 at page 2.) Thus, while citing these references for the teaching that HGF stimulates the proliferation, motility and growth of intestinal cells *in vitro,* the Examiner is

[2] Appellant believes that this dispute is an appealable matter. However, if the BPAI feels that this is a petitionable matter, Appellant respectfully requests that the arguments presented herein be considered as a petition under 37 C.F.R. § 1.181, requesting supervisory review of the Examiner's refusal to consider the Rule 131 Declaration to be sufficient. Please charge any petition related fees to Deposit Account No. 23-1951.

demanding that Appellant provide evidence of *in vivo* use of the invention in patients to reduce mucosal damage. The Examiner's reasoning is circular and flatly contrary to the MPEP, as explained in the Reply to Final Office Action dated January 25, 2005 at pages 7-8.

According to MPEP § 715.02:

> [w]here the differences between the claimed invention and the disclosure of the reference(s) are so small as to render the claims obvious over the reference(s), **an affidavit or declaration under 37 CFR 1.131 is required to show no more than the reference shows**. In other words, where the examiner, in rejecting a claim under 35 USC 103, has treated a claim limitation as being an obvious feature or modification of the disclosure of the reference(s) relied upon, without citation of a reference which teaches such a feature or modification, a 37 CFR 131 affidavit or declaration may be sufficient to overcome the rejection even if it does not show such feature or modification. (emphasis added)

Therefore, in accordance with MPEP § 715.02, the Rule 131 Declaration clearly establishes the prior invention of at least the same and actually more than the teachings as the cited references of Zushi, Ishii and Halttunen. Specifically, for example, the Rule 131 Declaration evidence establishes that the administration of an effective dose of HGF was shown to stimulate growth and proliferation of intestinal cells *in vivo* before May 1996, the earliest publication date of the cited references of Zushi, Ishii and Halttunen. (Rule 131 Declaration at ¶8.)

Thus, while the Examiner relies upon the *in vitro* teachings of the cited references to allege obviousness of the claimed invention to reduction of mucosal damage of the intestine, he appears to require Appellant not only to show *in vivo* data, which Appellant has done, but also to show data demonstrating the reduction of intestinal mucosal damage. This sort of circular reasoning is exactly what MPEP § 715.02 is designed to avoid. The Examiner cannot properly find the teachings of HGF inducing cell growth and proliferation in *in vitro* cell culture systems

in the prior art sufficient to show obviousness and, at the same, require Appellant to show anything more than that to remove the references.

Accordingly, Zushi, Ishii and Halttunen do not constitute prior art as shown by the Rule 131 Declaration, which evidences that Appellant invented at least the same teachings of the cited references prior to the earliest publication date of the cited references to Zushi, Ishii, and Halttunen.

b. Even Without the Rule 131 Declaration The Claimed Inventions Distinguish Over the Cited Prior Art

Although Zushi, Ishii and Halttunen are not valid prior art references, claims 7 and 21 easily distinguish over the prior art of record even if the three references are not removed. None of the applied references, either singly or in combination, teaches or suggests each and every limitation of claims 7 and 21. Thus, even if the combination of Zushi, Ishii, Fukamachi and Halttunen were proper, this combination would still fail to disclose or suggest at least the limitation to decreasing mucosal damage by administering an effective dose of HGF. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness.

More specifically, none of the cited references disclose or suggest administering HGF to a patient to ***decrease mucosal damage***, *e.g.,* by reducing inflammation or inflammatory mediators as disclosed in the specification. Instead, the references cited by the Examiner are only directed to the ***proliferation*** of intestinal epithelial cells in *in vitro* cell culture systems. In particular, Zushi is directed to intestinal restitution (wound resealing) in cell culture, Ishii is directed to intestinal cell proliferation and motility using *in vitro* systems, Fukamachi is directed to stimulated gastrointestinal epithelial growth in primary cultures, and Halltunen is directed to accelerated proliferation rate of T84 culture cells.

The Examiner's rejection and reasoning in response to our arguments are primarily directed to cell growth and proliferation. (*See* Final Office Action at page 3 stating "[t]he rejection combined several references to demonstrate that HGF has similar proliferative effect on different cell systems" and at page 4 stating "[t]he references used in the rejection demonstrate that HGF causes proliferation of intestinal cells.") Evidently, the Examiner has assumed that the only primary mechanism by which HGF is effective in inflammatory bowel disease is through cellular proliferation. On the other hand, the Examiner's response that the "instant claims are not drawn to any particular cellular mechanism [i.e., cellular proliferation]" is inconsistent with his rationale and does not address Appellant's arguments. (*See id.* at 5.) Again, claims 7 and 21 are directed to decreasing intestinal ***mucosal damage***, which not only includes reducing and preventing gross and histological lesions in a patient but also reducing intestinal inflammation and inflammatory mediators in a patient. *See, e.g.,* Specification at page 3, lines 18-21, which states "...administering HGF to subjects characterized as having IBD reduces the gross and histologic lesions...[and] reduces the gene expression of inflammatory mediators such as TNF-α and INF-γ in these subjects."

Moreover, contrary to the Examiner's allegations, the *in vitro* results of the cited art references cannot be translated to *in vivo* effects. (Final Office Action at page 3.) Specifically, the Examiner argued that the combined references "demonstrate that HGF has [a] similar proliferative effect on different cell systems each of which is an adequate model of *in vivo* conditions." (*Id.*) Appellant vigorously disagrees. Most importantly, the *in vitro* systems used in all of the Examiner's cited references are immortalized cells, grown in nonphysiological conditions, none of which have been influenced by the pathological conditions of infection or inflammation that frequently occur in patients afflicted with inflammatory bowel disease. The

Examiner cites no teaching prior to Appellant's discovery that HGF reduced mucosal damage. Therefore, it is scientifically, clinically and logically inaccurate to suggest that the results of *in vitro* cell culture would lead those of ordinary skill in the art to conclude that these results would provide evidence of the benefit to the clinical disorders or diseases of the intestine that are caused by infection, inflammation, or immunological disorders. At most, the references provide an invitation to try, which is clearly recognized as not being the standard for patentability. (*See, e.g.*, MPEP § 2145(X)(B).)

To support his obviousness argument, the Examiner also has alleged that the "Applicant argues that neither of the references teaches increase in the intestinal absorptive functions and intestinal mass." Nowhere in this application has Appellant made such an argument. Here, the Examiner relies upon arguments copied verbatim from an Office Action related to the parent case filed in 1996 that are not applicable here.

Finally, the Examiner has alleged that "after discussing the claimed subject matter in the parent case, the applicant agreed to limit claim language to an embodiment of increasing intestinal absorptive functions and intestinal tissue mass beyond the normal adaptive response." (Final Office Action at page 5.) Although it was agreed to amend the claims as such, it was also agreed to limit the scope of the claims to other *in vivo* conditions such as an intestinal inflammatory process. Accordingly, the same *in vivo* conditions that were incorporated into the claims of the parent case have been incorporated into the pending claims of this application. Indeed, the rejections of the claims in the parent application, now U.S. Patent No. 5,972,887, were withdrawn by the Examiner because the cell culture data could not be extrapolated to mucosa undergoing the process of intestinal adaptation. (*See, e.g.*, Amendment After Final for U.S. Application Serial No. 08/932,391 dated April 21, 1999 at page 6.) Similarly, the cell

culture data presented in the cited references here cannot be extrapolated to the *in vivo* histology, pathology or the results obtained with HGF in a model of immunologically induced bowel disease of the invention. Therefore, the Appellant respectfully submits that the claims of this application patentably distinguish over the prior art relied upon by the Examiner, even if the references are considered on their merits.

Accordingly, Appellant respectfully requests that the Examiner's rejection of claims 7 and 21 under 35 U.S.C. § 103(a) over the Zushi, Ishii, Fukamachi and Halttunen references be reversed.

2. Rejection of Independent Claim 26

The final rejection of claim 26 should also be reversed for all of the reasons given above for reversing the rejection of claims 7 and 21. Moreover, the rejection of claim 26 should be reversed for the additional reason that none of the prior art relied upon by the Examiner discloses or suggests the specific limitations of claim 26 requiring an "effective dosage range of HGF is about 30 μg/kg body weight/day to about 300 μg/kg body weight/day." This dosage, when used in combination with the subject matter recited in claim 26 is not disclosed or suggested by the applied references. Accordingly, the rejection of claim 26 should be reversed.

3. Rejection of Dependent Claims 9, 22 and 28

The rejection of claims 9, 22 and 28 under 35 U.S.C. § 103(a) as being unpatentable over Zushi, Ishii, Fukamachi and Halttunen is in error and the decision of the Examiner to finally reject these claims should be reversed for the following additional reasons. Dependent claims 9, 22 and 28 require, *inter alia*, that the administration of HGF is performed systemically.

None of the references discussed above, even if they all constituted prior art, whether taken singly or in combination, disclose or suggest that the administration of HGF is performed

systemically. As discussed above, the applied references are only directed to *in vitro* systems. In particular, for example, Zushi is directed to intestinal restitution (wound resealing), Ishii is directed to intestinal cell proliferation and motility using *in vitro* systems, Fukamachi is directed to stimulated gastrointestinal epithelial growth in primary cultures, and Halltunen is directed to accelerated proliferation rate of T84 cells. Thus, the rejection of claims 9, 22 and 28 over the Zushi, Ishii, Fukamachi and Halttunen references should be reversed.

4. The Rejection of Dependent Claims 10, 23 and 29

The rejection of claims 10, 23 and 29 under 35 U.S.C. § 103(a) as being unpatentable Zushi and Ishii and Fukamachi and Halttunen is in error, and should be reversed for the following additional reasons. Dependent claims 10, 23 and 29 require, *inter alia*, that the administration of HGF is performed lumenally.

As discussed above, the cited references are only directed to *in vitro* systems, and therefore, do not disclose or suggest lumenal administration of HGF. Accordingly, the rejection of claims 10, 23 and 29 should be reversed for this additional reason.

5. Rejection of Dependent Claims 11, 12, 24, 25 and 30

The rejection of claims 11, 12, 24, 25 and 30 under 35 U.S.C. § 103(a) as being unpatentable over Zushi, Ishii, Fukamachi and Halttunen is in error, and should be reversed for the following additional reasons. Dependent claims 11 and 24 require, *inter alia*, that the effective dosage range of HGF is about 30 μg/kg body weight/day to about 300 μg/kg body weight/day. Dependent claims 12, 25 and 30 require, *inter alia*, that the effective dose of HGF is about 150 μg/kg body weight/day.

The references applied by the Examiner only provide HGF dosage ranges applicable to *in vitro* cell culture studies. It is illogical and without basis to suggest that the dose of HGF used in

in vitro cell culture studies could be simply extrapolated by one skilled in the art to arrive at the effective HGF dosage ranges to be administered to a patient. The Examiner has cited no evidence of any *in vitro* model that correlates to the clinical model contemplated by the claimed inventions, i.e., reducing mucosal damage by administering an effective dose of HGF. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness for the subject matter of these claims. Thus, the rejection of claims 11, 12, 24, 25 and 30 over Zushi, Ishii, Fukamachi and Halttunen should be reversed.

6. Rejection of Dependent Claim 27

The rejection of claim 27 under 35 U.S.C. § 103(a) as being unpatentable over Zushi, Ishii, Fukamachi and Halttunen is in error, and should be reversed for the following additional reasons. Dependent claim 27 requires that the patient has a condition such as Chronic Ulcerative Colitis, Crohn's Disease, necrotizing enterocolitis, severe acute gastroenteritis, chronic gastroenteritis, cholera, chronic infections of the bowel, immunologic disorders affecting the intestine, immunodeficiency syndromes affecting the intestine, and HIV.

None of the references disclose or suggest the *in vivo* conditions as recited by claim 27. Thus, the rejection of claim 27 should be reversed.

7. Rejection of Dependent Claims 31, 32 and 33

The rejection of claims 31, 32 and 33 under 35 U.S.C. § 103(a) as being unpatentable over Zushi, Ishii, Fukamachi and Halttunen is in error, and should be reversed for the following additional reasons. Dependent claims 31, 32 and 33 make reference to the small intestine.

None of the references, even if they all constituted prior art, whether taken singly or in combination, disclose or suggest each and every limitation required by claims 31, 32 and 33. All of the cited references are only directed to *in vitro* cell culture systems and not *in vivo* conditions.

Accordingly, they do not disclose or suggest anything about the small intestine, and the rejection of these claims should be reversed for this additional reason.

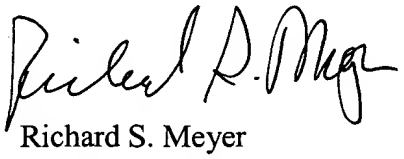
VIII. APPENDICES

The required appendices appear in the pages following the conclusion below.

CONCLUSION

Appellant respectfully submits that the Final Rejection of claims 7, 9-12 and 21-33 is in error for the reasons discussed above and prompt reversal thereof and remand to the Examiner for allowance is respectfully requested.

Respectfully submitted,



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RELATED PROCEEDINGS APPENDIX

As indicated above, there are no related proceedings.

CLAIMS APPENDIX

CLAIMS

A copy of each claim involved in the appeal is provided below.

Claims 1-6 (Cancelled).

7. A method for treating a patient having intestinal mucosal damage comprising decreasing the mucosal damage of the intestine by administering an effective dose of HGF to the patient wherein the patient has a condition selected from the group consisting of Chronic Ulcerative Colitis, Crohn's Disease, necrotizing enterocolitis, severe acute gastroenteritis, chronic gastroenteritis, cholera, and chronic infections of the bowel.

8. (Cancelled)

9. The method of claim 7 wherein the administration of HGF is performed systemically.

10. The method of claim 7 where the administration of HGF is performed lumenally.

11. The method of claim 7 wherein the effective dosage range of HGF is about 30 μg/kg body weight/ day to about 300 μg/kg body weight/day.

12. The method of claim 7 wherein the effective dose of HGF is about 150 μg/kg body weight/day.

13-20 (Cancelled).

21. A method for treating a patient having intestinal mucosal damage comprising decreasing the mucosal damage of the intestine by administering an effective dose of HGF to the patient wherein the patient has a condition selected from the group consisting of immunologic disorders affecting the intestine, immunodeficiency syndromes affecting the intestine, and HIV.

22. The method of claim 21, wherein the administration of HGF is performed systemically.

23. The method of claim 21, wherein the administration of HGF is performed lumenally.

24. The method of claim 21, wherein the effective dosage range of HGF is about 30 μg/kg body weight/day to about 300 μg/kg body weight/day.

25. The method of claim 21, wherein the effective dose of HGF is about 150 μg/kg body weight/day.

26. A method for treating a patient having intestinal mucosal damage comprising decreasing the mucosal damage of the intestine by administering an effective dose of HGF to the patient wherein the effective dosage range of HGF is about 30 μg/kg body weight/day to about 300 μg/kg body weight/day.

27. The method of claim 26, wherein the patient has a condition selected from the group consisting of Chronic Ulcerative Colitis, Crohn's Disease, necrotizing enterocolitis, severe acute

gastroenteritis, chronic gastroenteritis, cholera, chronic infections of the bowel, immunologic disorders affecting the intestine, immunodeficiency syndromes affecting the intestine, and HIV.

28. The method of claim 26, wherein the administration of HGF is performed systemically.

29. The method of claim 26, wherein the administration of HGF is performed lumenally.

30. The method of claim 26, wherein the effective of HGF is about 150 μg/kg body weight/day.

31. The method of claim 26, wherein the intestine includes the small intestine.

32. The method of claim 21, wherein the intestine includes the small intestine.

33. The method of claim 7, wherein the intestine includes the small intestine.

EVIDENCE APPENDIX

This section lists in the table below the evidence submitted pursuant to 37 U.S.C. §§ 1.130, 1.131, or 1.132, or any other evidence entered by the Examiner and relied upon by Appellant in this appeal. For each piece of evidence, the table includes a brief statement setting forth where in the record that evidence was entered by the Examiner. A copy of each piece of evidence is attached herewith as required by 37 U.S.C. § 41.37(c)(ix).

TABLE OF EVIDENCE RELIED UPON IN APPEAL

NO.	EVIDENCE	BRIEF STATEMENT
1	Declaration Under 37 C.F.R. § 1.131, filed January 25, 2005	Entered by the Examiner in the Advisory action dated March 22, 2005